



Original Article

Is There A Role of Glycated Hemoglobin for Predicting Major Adverse Cardiac Event in ST-Elevation Myocardial Infarction?

Muhammad Abusari^{1,2*}, Cholid Tri Tjahjono³, Dadang Hendrawan³, Yoga Waranugraha³, Ayu Asri Devi Adityawati³, Ratna Pancasari²

¹Department of Cardiology and Vascular Medicine, Dr. Soedono General Hospital, Madiun, Indonesia.

²Brawijaya Cardiovascular Research Center, Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.

³Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.

ARTICLE INFO

Keywords:

ST-elevation myocardial infarction;
Glycated hemoglobin;
Diabetes mellitus

ABSTRACT

Background : Coronary Artery Disease (CAD) especially ST-Elevation Myocardial Infarction (STEMI) is the leading cause of mortality worldwide. Hyperglycemia and diabetes mellitus are both prevalent among patients with STEMI admitted to the hospital. Glycated hemoglobin (HbA1c) is a marker of glucose control.

Objectives : We aimed to investigate the role of HbA1c as the predictor of major adverse cardiovascular events in STEMI patients.

Methods : This was a retrospective cohort study. STEMI patients visiting Saiful Anwar General Hospital were registered. Patients were divided into three groups based on the HbA1c level <6.5%; 6.5-8.4% and ≥8.5%; respectively. The primary endpoint was in-hospital Major Adverse Cardiovascular Events (MACE), including cardiac death, recurrent myocardial infarction (MI), recurrent revascularization, acute pulmonary edema, cardiogenic shock, malignant arrhythmia, and stroke.

Results: A total of 118 STEMI patients were included in this study, with distribution of 61 patients with HbA1c <6.5%, 25 patients with HbA1c 6.5-8.4%, and 31 patients with HbA1c ≥8.5%; respectively. The HbA1c level was associated with the history of diabetes mellitus (3.2% vs 36% vs 71%; $p = 0.000$) and random blood glucose level at hospital admission (140.71 ± 39.67 mg/dL vs 172.96 ± 53.43 mg/dL vs 366.61 ± 169.67 mg/dL; $p = 0.000$). The MACE among three groups was not significantly different (17.7% vs 20% vs 35.5%; $p = 0.149$).

Conclusion: Our study reveals that the HbA1c level at hospital admission is associated with the history of diabetes mellitus and random blood glucose at hospital admission. However, HbA1c could not predict MACE in STEMI patients

1. Introduction

In the past decades, rapid and sustained increase of prevalence of cardiovascular disease (CVD),¹ leads to a tremendous disease burden around the world. Acute coronary syndrome (ACS), which consist of Unstable Angina (UA), STEMI, and non-STEMI, is responsible for almost half of the CVD-associated morbidity.² STEMI is associated with acute total occlusion of the coronary arteries. It is the most high-risk emergency condition and still be the highest cause of mortality and morbidity. Revascularization strategy, including primary percutaneous coronary intervention (PPCI) and thrombolysis, must be performed to open acute total occlusion in the culprit artery and ensure adequate myocardial perfusion to prevent further myocardial damage.³ The mortality in STEMI patients can be affected by several factors, such as the history of previous MI, Killip class, advanced age, emergency

medical system (EMS)-based STEMI networks presence, time delay to treatment, treatment strategy, left ventricular ejection fraction (LVEF), number of diseased coronary arteries, diabetes mellitus, and renal failure.^{3,4}

Diabetes mellitus is a systemic metabolic disease that causes complications in microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (coronary artery disease, cerebrovascular disease, and peripheral artery disease).⁵ Adequate glycemic control, defined as HbA1c value $\leq 7\%$ has an essential role in preventing those dreadful complications.⁶ HbA1c reflects the mean glycemia level over the previous 8 to 12 weeks period.⁷ HbA1c levels also have a prognostic value for the onset of CVD in the future.⁸ However, the role of the HbA1c level in predicting the outcome of ACS is still unclear and needs to be proven. Several reports have shown that in patients with

*Corresponding author at: Brawijaya Cardiovascular Research Center, Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia
E-mail address: emailnya_aboe@yahoo.com (M. Abusari).

<https://doi.org/10.21776/ub.hsj.2020.001.03.4>

Received 9 September 2020; Received in revised form 12 September 2020; Accepted 24 September 2020

Available online 21 October 2020

2721-9976 / ©UB Press. All rights reserved.

STEMI, the HbA1c levels have a prognostic value. However, these reports data remain inconclusive.^{9,10} This study is aimed to investigate the role of HbA1c as the predictor of MACE in STEMI patients.

2. Methods

2.1. Design

We conducted a retrospective cohort study in Saiful Anwar General Hospital Malang, Indonesia, from May to August 2017. The investigation was approved by the institutional review board of Saiful Anwar General Hospital and conformed with all the principles outlined in the Declaration of Helsinki.

2.2. Study population

All STEMI patients from April 2015 to August 2017 were registered and included in this retrospective cohort study. The data about age, gender, STEMI characteristics, CVD risk factors, past medical history, vital signs, laboratory finding, medication, revascularization strategy, Killip class, Global Registry of Acute Coronary Events (GRACE) risk score, thrombolysis in myocardial infarction (TIMI) risk score, and MACE were collected from the medical records. The additional information was obtained via a phone call interview. The exclusion criteria included (1) incomplete data, (2) chronic kidney disease (CKD), and (3) anemia.

2.3. Exposure and Outcome

The exposure was the HbA1c level at hospital admission. HbA1c was obtained from peripheral venous blood samples taken at hospital admission. According to the HbA1c level, Patients were divided into three groups; <6.5% (group 1); 6.5-8.4% (group 2), ≥8.5% (group 3). The outcome measure was in-hospital MACE. MACE was defined as the composite of total cardiac death, recurrent MI, recurrent revascularization, acute pulmonary edema, cardiogenic shock, malignant arrhythmia, and stroke (Figure 1).

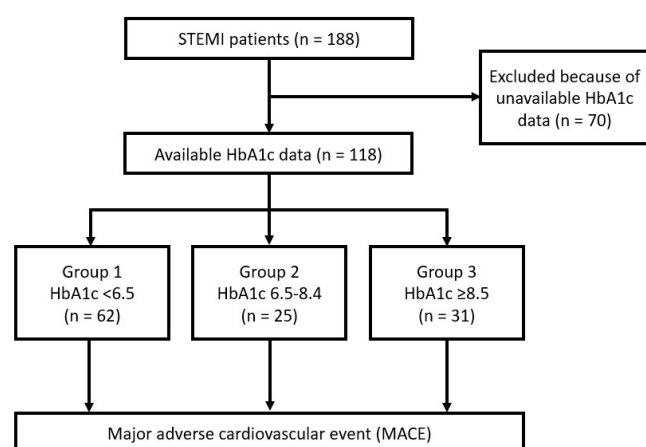


Figure 1. Study flowchart

2.4. Statistical Analysis

Categorical data were presented as number and its percentage. However, the numeric data were presented as mean and its standard deviation. Chi-square test was conducted for categorical data analysis. For normally distributed data, numeric data was analyzed using the analysis of variance (ANOVA) test. However, if the data abnormally distributed, the statistical analysis of numerical data was

conducted using the Kruskal Wallis test. The analysis was conducted using IBM SPSS version 22 software.

3. Result

3.1. Baseline Characteristics

In this retrospective cohort study, we successfully registered 188 STEMI patients. However, 70 patients were excluded due to one or more the following reasons: (1) incomplete data, (2) chronic kidney disease (CKD), or (3) anemia. Finally, a total of 118 STEMI patients were involved in the statistical analysis process with distribution: (1) 61 patients of HbA1c <6.5% (group 1); (2) 25 patients of HbA1c 6.5-8.4% (group 2); and (3) 31 patients of HbA1c ≥8.5% (group 3). The study flowchart is summarized in Figure 1.

Overall, baseline characteristic among the three groups were not significantly different. However, lower HbA1c level was more common in male patients (88.7% vs 80% vs 58.1%; $p = 0.003$) and cigarette smokers (77.4% vs 60% vs 51.6%; $p = 0.032$). HbA1c level also associated with previous history of diabetes mellitus (3.2% vs 36% vs 71%; $p = 0.000$), random blood glucose level at admission (140.71 ± 39.67 mg/dL vs 172.96 ± 53.43 mg/dL vs 366.61 ± 169.67 mg/dL; $p = 0.000$), and TIMI risk score ($p = 0.037$). The mean onset of STEMI was ranging from 7.52 to 8.83 hours and not all patients received revascularization therapy including PPCI or thrombolysis (Table 1).

Overall, medications given during in-hospital treatment were similar among the three groups. dual antiplatelet treatment (aspirin and P2Y12ADP inhibitor) and anticoagulant were given to all patients. The difference of angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), β -blocker, mineralocorticoid receptor antagonist (MRA), nitrate, and a statin administration among three groups were not significant ($p \geq 0.05$). The medication during in-hospital treatment is summarized in table 2.

MACE, including cardiac death, recurrent MI, recurrent revascularization, acute pulmonary edema, cardiogenic shock, malignant arrhythmia, and stroke was the endpoint of this study. Statistically, the MACE among three groups was not significantly different (17.7% vs 20% vs 35.5%; $p = 0.149$). MACE among the three groups is shown in figure 2.

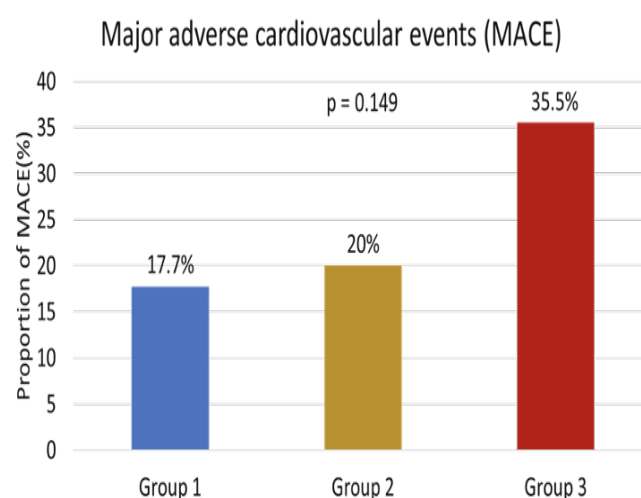


Figure 2. Major adverse cardiovascular events

Table 1. Baseline characteristics

Parameter	HbA1c < 6.5% n=62	HbA1c < 6.5% - 8.4% n=25	HbA1c ≥ 8.5% n=31	p-Value
Age	57.74 ± 9.23	60.88 ± 11.68	59.87 ± 10.35	0.359
Male	55 (88.7)	20 (80)	18 (58.1)	0.003
Systolic blood pressure	126.66 ± 34.59	134.12 ± 29.17	126.13 ± 40.40	0.628
Diastolic blood pressure	77.24 ± 19.02	83.28 ± 15.46	75.23 ± 26.16	0.319
Heart Rate	76.40 ± 21.36	78.12 ± 18.89	81.10 ± 24.91	0.622
CVD Risk Factors				
Family history of sudden death	3 (4.8)	0 (0)	3 (9.7)	0.262
Cigarette smoking	48 (77.4)	15 (60)	16 (51.6)	0.032
Diabetes Mellitus	2 (3.2)	9 (36)	22 (71)	0.000
Hypertension	32 (51.6)	15 (60)	21 (67.7)	0.324
Dyslipidemia	10 (16.1)	0 (0)	4 (12.9)	0.109
Past medical history				
Heart Failure	7 (11.3)	3 (12)	5 (16.1)	0.800
Stroke	1 (1.6)	2 (8)	1 (3.2)	0.332
COPD	0 (0)	1 (4)	0 (0)	0.156
Coronary Artery Disease	2 (3.2)	0 (0)	2 (6.5)	0.416
STEMI				
Onset	7.52 ± 7.20	8.28 ± 8.21	8.83 ± 7.29	0.105
Anterior STEMI	35 (56.5)	9 (36)	21 (67.7)	0.058
Primary PCI	12 (19.4)	4 (16)	6 (19.4)	0.930
Fibrinolytic	33 (53.2)	11 (44)	19 (61.3)	0.438
Killip Class				
I	43 (69.4)	18 (72)	19 (61.3)	0.489
II	3 (4.8)	1 (4)	0 (0)	
III	4 (6.5)	2 (8)	2 (6.5)	
IV	12 (19.4)	4 (16)	10 (32.3)	
TIMI Risk Score				
0-2	13 (21)	4 (16)	2 (6.5)	0.037
3-8	46 (74.2)	21 (84)	24 (77.4)	
9-14	3 (4.8)	0 (0)	5 (16.1)	
GRACE Risk Score				
≤108	17 (27.4)	5 (20)	4 (12.9)	0.195
109-140	25 (40.3)	8 (32)	13 (41.9)	
>140	20 (32.3)	12 (48)	14 (45.2)	

Laboratory findings

Hemoglobin	514.03 ± 1.29	14.3 ± 2.36	13.64 ± 1.65	0.317
Leucocyte	13045.6 ± 3248.25	14476.8 ± 5140.25	13199.35 ± 3661.12	0.276
Creatinine	1.18 ± 0.48	0.99 ± 0.4	1.31 ± 0.9	0.105
Random blood sugar	140.71 ± 39.67	172.96 ± 53.43	366.61 ± 169.67	0.000
Total cholesterol	176.53 ± 55.21	182.72 ± 41.29	181.42 ± 55.14	0.850
Triglyceride	143.19 ± 110.88	145.8 ± 61.65	162.32 ± 95.29	0.142
HDL	38.42 ± 15.23	38.76 ± 8.03	37.29 ± 11.77	0.900
LDL	121.34 ± 45.1	126.6 ± 32.07	120 ± 45.71	0.832

Note, data were presented in mean ± SD or n(%); HbA1c = The hemoglobin A1c; CVD = Cardiovascular disease; Aspartate aminotransferase; COPD = Chronic obstructive pulmonary disease; STEMI = ST-elevation myocardial infarction; PCI = Percutaneous coronary intervention; TIMI = Thrombolysis in Myocardial Infarction; GRACE = The Global Registry of Acute Coronary Events; HDL = high-density lipoproteins; LDL = low-density lipoproteins.

Table 2. Medical treatment during in hospital treatment

Parameter	HbA1c < 6.5% n=62	HbA1c < 6.5% - 8.4% n=25	HbA1c ≥ 8.5% n=31	p-Value
Anticoagulant	62 (100)	25 (100)	31 (100)	1.000
Aspirin	62 (100)	25 (100)	31 (100)	1.000
P2Y12ADP inhibitor	62 (100)	25 (100)	31 (100)	1.000
Nitrate	45 (72.6)	21 (84)	21 (67.7)	0.375
β-blocker	35 (56.5)	15 (60)	12 (38.7)	0.193
Statin	59 (95.2)	25 (100)	27 (87.1)	0.112
ACE inhibitor	44 (71)	19 (76)	17 (54.8)	0.182
ARB	2 (3.2)	2 (8)	2 (6.5)	0.608
Spironolactone	3 (4.8)	2 (8)	2 (6.5)	0.845

Note, data were presented in mean ± SD or n(%); HbA1c = The hemoglobin A1c; ACE = Angiotensin-converting enzyme; ARB = Angiotensin-receptor blockers.

4. Discussion

Since introduced in 1980, HbA1c has become a cornerstone of diabetes mellitus diagnostic criteria and treatment goals.¹¹ HbA1c reflects total blood glucose exposure to the red blood cells. The turnover of HbA1c depends on the red blood cell lifespan; therefore, it reflects the average plasma glucose over the previous 8 to 12 weeks.^{7,12} HbA1c level can be measured at any time. It does not need any specific preparation, such as fasting at least 8 hours before the blood sample is taken.¹³ In this study, lower HbA1c level more common in male patient (88.7% vs 80% vs 58.1%; $p = 0.003$). Our result did not support a previous study by Qinglin et al., which involved 18,265 patients. They revealed that in the general population, the HbA1c levels were influenced by sex and age. The HbA1c level in men was slightly higher than in women, and with increasing age, the levels

would also increase gradually.¹⁴ The possible explanations for this discrepancy were: (1) only STEMI patients were included, not the general population; and (2) smaller sample size.

This study found that the higher TIMI value was found in the group with higher HbA1c. It was because the TIMI value also contained components of (1) age; (2) Killip class; (3) anterior MI or left bundle branch block (LBBB); (4) systolic blood pressure; (5) heart rate; (6) weight; (7) prior angina; (8) diabetes mellitus; (9) hypertension, and (10) time to thrombolytic.¹⁵ Therefore, higher levels of HbA1c were found to be correlated with high TIMI value.

In this study, the history of diabetes mellitus was associated with increased levels of HbA1c at admission due to STEMI. A study by Timmer et al. obtained a similar result that patients admitted because

of ACS and high HbA1c levels were found in patients with a previous history of diabetes mellitus. Blood glucose level control is essential in diabetic patients. Poor glucose control before the onset of STEMI, as illustrated by high levels of HbA1c at admission, can cause many complications in diabetic patients.¹⁶ Pusuroglu et al. showed poor glucose control, as reflected by increased HbA1c levels, increased mortality, reinfarction, and stroke in diabetes mellitus patients in long-term monitoring.¹⁷ A long-term study from Hwang et al. revealed that tight blood glucose level control assessed using controlled HbA1c levels could reduce mortality, MI, and stroke.¹⁸

In this study, we found a close relationship between an increase in blood glucose and HbA1c levels. Hyperglycemia at hospital admission is a common comorbid in STEMI.¹⁹ This condition can occur in patients with diabetes mellitus and patients with a history of diabetes mellitus. The prevalence of diabetes mellitus ranged from 12.4% to 25% of hyperglycemia patients at hospital admission.²⁰ Hyperglycemia on admission is a mortality predictor in MI patients.²¹ During hyperglycemia, the cytokines level is increased, especially tumor necrosis factor-alpha (TNFα). These cytokines caused endothelial dysfunction and reduced myocardial contractility.^{22,23} In patients with STEMI who are accompanied by hyperglycemia signs, it will be challenging to dig about the previous history of DM. In this study, blood glucose levels on admission to the hospital were not an independent predictor of mortality. It may be regarding the comprehensive management of hyperglycemia in STEMI patients, and multifactorial causes of mortality.

This study did not reveal a significant relationship between HbA1c levels on admission with clinical outcomes, although there was an increased rate of worsening clinical outcomes among three groups (17.7% vs. 20% vs. 35.5%; $p = 0.149$). Other studies by Timmer JR et al. and Cakmak et al. revealed that the HbA1c value failed to predict in-hospital mortality although data on higher mortality were found, after adjusting several cardiovascular risk factors. Therefore, it was concluded that HbA1c levels were not a strong predictor of increased long-term mortality.^{16,24} A study, including a large population by Optimal Therapy in Myocardial Infarction With Angiotensin II Antagonist Losartan (OPTIMAAL), also concludes that HbA1c levels were not a predictor of mortality in patients with diabetes mellitus.²⁵

Our study had several limitations. First, the data in this study were obtained from the medical record, which may cause errors in recording. Second, data were obtained from a single-center; therefore, they could not represent the overall population. Third, our study involved a small number of samples. Fourth, we had several confounding factors that could not be managed, for example, revascularization strategy. Not all patients included in this study received revascularization. Some parameters in the previous studies that were considered to be the cause of mortality were not proven to cause mortality in this study. The possible explanation was the data obtained only described the initial conditions at hospital admission. Some patients also suffered from mechanical complications due to STEMI, which may have a more significant role in mortality than just the HbA1c level value. Some patients are also on a ventilator due to respiratory failure, which may have a more significant role in patient mortality than the initial HbA1c value.

4. Discussion

Our study revealed that the HbA1c level at hospital admission is associated with the history of diabetes mellitus and random blood glucose at hospital admission. However, the HbA1c level at hospital admission could not predict MACE in STEMI patients.

6. Declarations

6.1. Ethics Approval and Consent to participate

This study was approved by local Institutional Review Board, and all participants have provided written informed consent prior to involve in the study.

6.2. Consent for publication

Not applicable.

6.3. Availability of data and materials

Data used in our study were presented in the main text.

6.4. Competing interests

Not applicable.

6.5. Funding source

Not applicable.

6.6. Authors contributions

Idea/concept: MA. Design: MA. Control/supervision:CT, DH, YW. Data collection/processing: MA, AAD, RP. Extraction/Analysis/interpretation: VK. Literature review: CT, DH, YW. Writing the article: MA, AAD, RP. Critical review: CT, DH, YW. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

6.7. Acknowledgements

We thank to Brawijaya Cardiovascular Research Center.

References

- Joshi R, Alim M, Kengne AP, et al. Task shifting for non-communicable disease management in low and middle income countries—a systematic review. *PloS one* 2014;9:e103754.
- Zhao Z, Winget M. Economic burden of illness of acute coronary syndromes: medical and productivity costs. *BMC health services research* 2011;11:35.
- Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *European heart journal* 2018;39:119-77.
- Dai X, Kaul P, Smith Jr SC, Stouffer GA. Predictors, treatment, and outcomes of STEMI occurring in hospitalized patients. *Nature Reviews Cardiology* 2016;13:148.
- Turner RC. The UK prospective diabetes study: a review. *Diabetes care* 1998;21:C35-C8.
- Haghighatpanah M, Nejad ASM, Haghighatpanah M, Thunga G, Mallayasamy S. Factors that correlate with poor glycemic control in type 2 diabetes mellitus patients with complications. *Osong public health and research perspectives* 2018;9:167.
- Lenters-Westra E, Schindhelm RK, Bilo HJ, Slingerland RJ. Haemoglobin A1c: Historical overview and current concepts. *Diabetes Research and Clinical Practice* 2013;99:75-84.
- Yeung SLA, Luo S, Schooling CM. The impact of glycated hemoglobin (HbA1c) on cardiovascular disease risk: a Mendelian randomization study using UK Biobank. *Diabetes Care* 2018;41:1991-7.
- Corpus RA, O'Neill WW, Dixon SR, Timmis GC, Devlin WH. Relation of hemoglobin A1c to rate of major adverse cardiac events in

- nondiabetic patients undergoing percutaneous coronary revascularization. *The American journal of cardiology* 2003;92:1282-6.
- 10 Hadjadj S, Coisne D, Mauco G, et al. Prognostic value of admission plasma glucose and HbA1c in acute myocardial infarction. *Diabetic medicine* 2004;21:305-10.
 - 11 Massi-Benedetti M. Changing targets in the treatment of type 2 diabetes. *Current medical research and opinion* 2006;22:S5-S13.
 - 12 Leow MKS. Glycated Hemoglobin (HbA1c): Clinical Applications of a Mathematical Concept. *Acta Informatica Medica* 2016;24:233.
 - 13 Committee IE. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes care* 2009;32:1327-34.
 - 14 Ma Q, Liu H, Xiang G, Shan W, Xing W. Association between glycated hemoglobin A1c levels with age and gender in Chinese adults with no prior diagnosis of diabetes mellitus. *Biomedical reports* 2016;4:737-40.
 - 15 Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation: an intravenous nPA for treatment of infarcting myocardium early II trial substudy. *Circulation* 2000;102:2031-7.
 - 16 Timmer J, Ottervanger J, Bilo H, et al. Prognostic value of admission glucose and glycosylated haemoglobin levels in acute coronary syndromes. *Journal of the Association of Physicians* 2006;99:237-43.
 - 17 Pusuroglu H, Akgul O, Cakmak HA, et al. Long-term prognostic value of admission haemoglobin A1c (HbA1c) levels in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Postępy w Kardiologii Interwencyjnej= Advances in Interventional Cardiology* 2014;10:166.
 - 18 Hwang JK, Lee SH, Song YB, et al. Glycemic control status after percutaneous coronary intervention and long-term clinical outcomes in patients with type 2 diabetes mellitus. *Circulation: Cardiovascular Interventions* 2017;10:e004157.
 - 19 Bruno RR, Kelm M, Jung C. Spotlight on comorbidities in STEMI patients. *Endocrinology, Diabetes & Metabolism* 2020;3:e00102.
 - 20 Clement S, Braithwaite SS, Magee MF, et al. Management of diabetes and hyperglycemia in hospitals. *Diabetes care* 2004;27:553-91.
 - 21 Sanjuán R, Núñez J, Blasco ML, et al. Prognostic implications of stress hyperglycemia in acute ST elevation myocardial infarction. Prospective observational study. *Revista Española de Cardiología (English Edition)* 2011;64:201-7.
 - 22 Bakker W, Eringa EC, Sipkema P, van Hinsbergh VW. Endothelial dysfunction and diabetes: roles of hyperglycemia, impaired insulin signaling and obesity. *Cell and tissue research* 2009;335:165.
 - 23 Mapanga RF, Essop MF. Damaging effects of hyperglycemia on cardiovascular function: spotlight on glucose metabolic pathways. *American Journal of Physiology-Heart and Circulatory Physiology* 2016;310:H153-H73.
 - 24 Cakmak M, Cakmak N, Cetemen S, et al. The value of admission glycosylated hemoglobin level in patients with acute myocardial infarction. *Canadian journal of cardiology* 2008;24:375-8.
 - 25 Gustafsson I, Kistorp CN, James MK, et al. Unrecognized glycometabolic disturbance as measured by hemoglobin A1c is associated with a poor outcome after acute myocardial infarction. *American heart journal* 2007;154:470-6.